REMARKS/ARGUMENTS

The Rejections Under 35 USC § 112

The Office Action rejects the method claims alleging that they are not enabled.

In a proper enablement rejection, which is not made here, first and foremost, a specification disclosure which "contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Emphasis added.) *In re Marzocchi*, supra. "The PTO must have adequate support for its challenge to the credibility of applicant's statements of utility". (The quoted statement was made in the context of enablement, i.e., the how-to-use requirement of the first paragraph of section 112.) See also *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981). The only relevant concern of the Patent Office should be over the truth of assertions relating to enablement. The first paragraph of section 112 requires nothing more than objective enablement. See *In re Marzocchi, supra.*

The Examiner has not established any basis to doubt objective enablement. The Examiner has also provided no support for establishing that one of ordinary skill would doubt the objective truth of the asserted utility, which is enabled by the specification. The rejection therefore is improper under *In re Marzocchi*.

The claims rejected are directed to the treatment of a cancerous cell growth mediated by raf kinase, i.e., to treatments that are not objectively doubtable. Doubt has been held reasonable only where, for example, the invention has been characterized as "highly unusual," *In re Houghton*, 433 F.2d 820 (CCPA 1970), as "incredible," *In re Citron*, 325 F.2d 248, (CCPA 1963), or as "too speculative," *In re Eltgroth*, 419 F.2d 918 (CCPA 1970). Applicants on the first two pages of the specification discuss numerous prior art references, which establish that it is known in the art that many cancers are mediated by raf. Because compounds having similar therapeutic activities are known in the art, the existence of a new class of compounds having the claimed activities is not objectively doubtable, i.e., not "highly unusual," "incredible," and/or "too speculative."

The Office Action acknowledges that the specification points to various prior art literature publications on how to treat solid tumors and on the correlation of in vivo and in vitro inhibitory

growth and the inhibition of ras kinase, but states that "the compounds of the claimed subject matter are vastly different than the cited prior art." Once again, applicants remind the Examiner, that the first paragraph of section 112 requires nothing more than objective enablement. The Patent Office has provided no basis for doubting the objective truth of the asserted utility. The invention of a new class of compounds, even if the compounds may be different than prior art compounds, that have activities on raf are not objectively doubtable since other compounds having the similar activities are known in the art.

In any event, applicants provide adequate guidance in the specification for one of ordinary skill in the art as to how to proceed in using the claimed invention. Applicants teach the compounds of the invention which are enabled, teach that the compounds act on raf, teach how the activities of individual compounds can be determined, teach the activities of the exemplified compounds, and provide guidance as to administration modes and amounts throughout the specification. Thus, the allegation that "the specification does not give any guidance as to the method of treating cancerous cell growth using the compounds of the instant claims" has no basis.

The Office Action nevertheless alleges that "there is no known anticancer agent, which is effective against cancer such as pancreatic, lung and colon, thyroid or bladder or that matter." There is no basis for this allegation. Applicants attach a copy of *Lemoine et al.*, "Overview of ras oncogenes and their clinical potential," Chapter 10, SciSearch 2000:751594, which teaches that pancreatic cancer, acute myeloid leukemia, colorectal cancer, thyroid cancer, and non-small-cell lung carcinoma are highly associated with the ras/raf kinase pathway, that bladder cancer, etc., are associated with the ras/raf kinase pathway to an intermediate extent, and that a variety of cancers are less associated with ras/raf. See table 10.2 on page 89 of the publication. Also attached is a copy of *Ravi et al.*, "Activated Raf-1 causes growth arrest in human small cell lung cancer cells," J. Clin. Invest., Vol. 10, No. 1, Jan. 1998, 153-159, for which the title speaks for itself.

The Office Action incorrectly alleges that "applicants have even failed to provide any in vitro data, which can be extrapolated to the in vivo data." Applicants respectfully disagree and point to page 174, which teaches in the biological examples section that in the in vitro raf kinase assay, all compounds exemplified, which are 144 compounds (see the tables), displayed IC_{50}sof

between 1 nM and 10 μM. Thus, there is quite significant amount of in vitro data in the specification. While applicants did not list each of the exemplified compound's IC_{50}, such is not required, and as a matter of fact no examples at all are required (see discussion below). One of ordinary skill in the art knows from what is taught that these compounds have activities in the range provided.

The Office Action also alleges that "there is not a single example provided which can point out to the treatment of the solid tumor." However, an applicant is not required to demonstrate examples of treatments of diseases that are claimed. See *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1441 (Fed. Cir. 1995), stating that the "stage at which an invention in this field becomes useful is well before it is ready to be administered to humans," e.g., well before an example of treatment stage.

Additionally, there is no requirement for any examples in patent applications generally. See, for example, *Marzocchi*, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP is in agreement with this by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

Appellants point the PTO's attention to the facts of *In re Bundy*, supra, which are relevant here. The specification in that case disclosed only that the compounds of the invention possess activity similar to E-type prostaglandins, i.e., no examples were provided. Nevertheless the court found that sufficient guidelines as to use were given in the disclosure. The court held that "what is necessary to satisfy the how-to-use requirement of section 112 is the disclosure of some activity coupled with knowledge as to the use of this activity." (Emphasis added.) Appellants have done at least that in the present case and even more, and thus, satisfied the how-to-use requirement of section 112.

Reconsideration of this rejection is respectfully requested.

The Rejection Under 35 USC § 103

The Office Action maintained the rejection of the compound claims over Widdowson. Applicants' arguments from the previous reply on this issue are fully incorporated herein.

The compounds of the reference are distinct from the compounds of the present claims as

discussed in the previous reply for at least the reasons discussed with respect to claim 27, i.e., because the structure of the compounds are different.

The groups -M-L^1 of the compounds now claimed are not ortho-positioned on the phenyl ring neighboring the urea group as is the X_1R_2 group of Widdowson. All of the compounds claimed herein have hydrogen on both ortho-positions of the phenyl ring. Replacing the substituent "X_1R_2"of Widdowson with hydrogen would not be obvious in that Widdowson teaches that the "X_1R_2"substituent is required at this position.

Additionally, Widdowson requires that R_2 of the group X_1R_2 have a functional moiety that provides ionizable hydrogen having a pKa of 10 or less. The compounds of the present invention do not require such an ionizable hydrogen and in fact, all compound claims except claims 27 and 34 define compounds which have a pKa greater than 10. The compounds of claims 1-11, 13, 14 and 20-26 are structurally distinct from the compounds of Widdowson based on this functional limitation. It would not be obvious to ignore the requirements of Widdowson and prepare compounds with a pKa of greater than 10. Furthermore, there is neither evidence nor a hint or suggestion that positioning the group X_1R_2 at a position other than ortho will enable the functional moieties defined in the application to provide ionizable hydrogen having a pKa of 10 or less.

Most of the groups -M-L^1, which can be selected for R^3, R^4 and R^5 of the compounds claimed herein, have substituents on L^1 which are distinct from the functional groups said by Widdowson to provide ionizable hydrogen having a pKa of 10 or less for R (see page 4, lines 35-38). The groups -M-L^1 for these compounds are distinct in composition from the X_1R_2 groups of Widdowson and therefore, these compounds are not position isomers. Claim 34 defines only compounds where all M-L^1 groups are distinct in composition from the X_1R_2 groups of Widdowson. The compounds of claim 34 are not position isomers of the compounds of Widdowson and are clearly unobvious in view of this reference.

A small overlap exists between the substituents defined for L^1 herein and the functional groups defined for R of Widdowson which is the moiety "OH." As mentioned above, all claimed compounds where L^1 is substituted by OH are distinct from those of Widdowson since the hydroxy substituted group –M-L^1 is not at the ortho position of the phenyl ring. Even if the pKa

requirements within claims 1-11, 12-14 and 20-26 are ignored and eliminated, as is the case for claim 27, the compounds defined are unobvious. The compounds of claim 27 cannot be considered obvious position isomers of the reference's formula Ib since there is no direction or motivation to make all the right choices and selections which are necessary from the references generic formula to arrive at a M-L^1 group consistent with this invention and place it at a meta- or para-position on the phenyl group.

The reference provides not a single example of a compound of the formula Ib where R_2 is substituted by OH. Only a list of possible substituents is provided on page 21 of the reference.

The CCPA set forth the test for obviousness for position isomers when stating that

> The fact that a position isomer of a compound is known is some evidence of the obviousness of that compound. Position isomerism is a fact of close *structural* similarity which is to be taken into consideration with all other relevant facts in applying the test of obviousness under 35 U.S.C. 103. It is the closeness of the relationship rather than the mere name, or, here, position number, which is significant, and which gives rise to an inference that the claimed compound is obvious.
>
> A compound is not, however, merely a structural formula; its properties as part of the whole must be considered. The similarity of *properties* of a reference compound as compared with a claimed compound gives rise to an even stronger inference of obviousness than that of structural similarity alone, and conversely, where the properties are different, they imply non-obviousness, when they are unexpected. (Citations omitted.)

See *In re Mehta*, 146 USPQ 284 (CCPA 1965).

In the *Mehta* case, obviousness was found since the "same moiety" substituted in a different position was the only difference between the reference compounds and the claimed compounds and the properties of the reference compounds and the claimed compounds were the "same." That is not the case here. Both the activity and uses of the compounds are different for the claimed compounds than the uses and activity of the reference compounds, i.e., the reference compounds are said to be useful for the treatment of chemokine mediated diseases, while the claimed compounds are useful for the treatment of a cancerous cell growth mediated by raf kinase. Nothing in the reference teaches or suggests that the compounds of the claims possess the claimed activity. Thus, under the test laid down by the court in *Mehta*, the different uses imply non-obviousness. Other cases that followed *Mehta* on the obviousness of position

isomers, concerned situations where the uses of the compounds were the same. See *In re Kilsheimer*, 146 USPQ 491 (CCPA 1965) and *In re Crounse*, 150 USPQ 554 (CCPA 1966). Nothing in the case law provides support for the Office Action's position over the rejected claims.

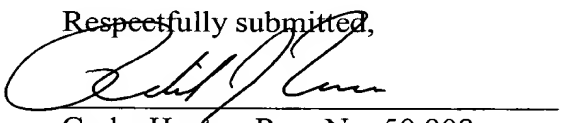
As mentioned above, several independent claims further distinguish the reference in that the pKa values of the claimed compounds are different than those of Widdowson's compounds. This pKa limitation in the claims cannot be ignored as this limitation helps eliminate overlap with Widdowson. It clearly would not be obvious to prepare diphenyl urea compounds with a pKa value greater than 10 based on this reference.

Because nothing in the reference teaches or suggest compounds of the claims, the claims of the present application are not obvious.

Reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



Csaba Henter, Reg. No. 50,908
Richard J. Traverso, Reg. No. 30,595
Attorney/Agents for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: BAYER-6P1

Date: **February 2, 2005**

K:\Bayer\6 P1\Reply Jan 2005.doc